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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/659,178	09/09/2003	David Jonathan Madge	2713.0090006	7469

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EXAMINER	
VALENROD, YEVGENY	
ART UNIT	PAPER NUMBER
1621	
MAIL DATE	DELIVERY MODE
10/14/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/659,178	MADGE ET AL.	
	Examiner	Art Unit	
	YEVEGENY VALENROD	1621	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 July 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14-22,37,38,40-55,57 and 59-72* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14-22,37,38,40-55,57 and 59-72* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 September 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/27/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The following is a Final office action in application # 10/659,178. Amended claims submitted by the applicant on 7/30/08 are acknowledged.

Remarks submitted on 7/30/08 have been fully considered.

The declaration by Dr. Marsden under 37 C.F.R. § 1.132(the Marsden declaration) has been fully considered.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 14-22, 37, 38, 40-55, 57, 59-72 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rewinkel et al. (Current Pharmaceutical Design, 1999, 5, 1043-1075) in view of de Nanteuil et al. (US 5,814,622) and in further view of Adams et al. US 5,780,454).

Instant claims 1-18, 21, 22, 23, 26-28 and 30-36 are directed to a pharmaceutically acceptable base addition salt of a boronic acid of formula (I) in claim 1, or formula (II) in claim 14 and to formulation of the said salt in claims 26-28.

Scope of prior art

Rewinkel et al. teach a compound of formula 21 (page 1052, bottom left of Table 3). The said compound is a boronic acid that has the methoxyalkyl substituent for R^9 in the instant claim 1, a Pro amino acid residue (Which is also referred to as imino acid in the art), which satisfies the structural limitation of claim 17, a hydrophobic moiety presented by the diphenylalanine residue, and a protected N-terminal amine group. Renkwel et al. Provide Ki for thrombin inhibition in the table on the bottom of page 1052. Compound 21, has Ki of 14 nM, which is below 100nM as claimed in claims 7 and 28.

Ascertaining the difference between prior art and the instant claims

Rewinkel et al. teach the organic component of the instantly claimed organoboronic acid salt. They also teach the boronic acid attached to the organic component in a position consistent with the structural limitations of the instant claims. However, they fail to teach the pharmaceutically acceptable salt of the boronic acid.

Secondary references

Nanteuil et al. describe compound of formula (I/g) (organoboronic acid) and pharmaceutically acceptable salts thereof (column 6, lines 20-36). The pharmaceutically acceptable salts include both base and acid addition salts. In Column 3, lines 32-34 Nanteuil et al. describe examples of counterions for base addition salts. Said examples include Sodium, Potassium and amines.

Adams et al. teach boronic acid compounds of formula 1(a) which encompass the instantly claimed compounds. Adams et al. also teach pharmaceutically acceptable

base addition salts (column 9, lines 47-48) which include various alkaline metal, alkaline earth metal and amine (including amino acids) salts (column 9 lines57-65).

Motivation and obviousness

It is obvious to form salts from known acids. In re Williams, 89 USPQ 396 (CCPA 1951). Rewinkel et al. teach compound 21, which is the acid of the instantly claimed pharmaceutically acceptable salt. At the time the instant invention was made, one of ordinary skill in the art looking to alter the permeability, solubility, or other physiological properties commonly associated with producing pharmaceutically acceptable salts of known acid (see Davies et al, The pharmaceutical journal, 2001, Vol 266, p 322-323; particularly page 322, column 1, first paragraph) would have been motivated to prepare a salt of the organoboronic acid 21 described by Rewinkel et al. Such a modification would not be new to the art. Nanteuil et al. describe pharmaceutically acceptable salts of organoboronic acids and thus provide an expectation of success for performing the said modification. Nanteuil et al. do not limit themselves to the counterion examples that are listed in column 3 lines 32-34. They specifically mention that these examples are provided without any limitation. One of ordinary skill in the art would be motivated to produce various pharmaceutically acceptable salts in order to achieve the desired properties of the pharmaceutical agent. Pharmaceutically acceptable salts of organoboronic acids salts include alkaline metal salts, alkaline earth metal salts (including calcium) and amine salts (Adams et al. US 5,780,454; column 9, lines 57-65). In the absence of some unexpected properties for the base addition salts of organoboronic acids of the instantly claimed compounds, the

invention is seen to be prima facie obvious in view of the prior art of record and the case law cited herein.

Reply to applicants' remarks

Consideration of the Wu reference

Applicant has argued that Wu reference would lead one skilled in the art away from making a boronic acid salt.

Examiner disagrees. Wu et al. study the decomposition of a single boronic acid compound that falls outside of the instant claims. Wu do not intend on making the salt of the said compound, but rather are more interested in resulting decomposition products. Wu et al. store the solution comprising NAOH and the target compound at $70^{o}C$. One skilled in the art would not be demotivated from making boronic acid salts in view of Wu. Wu do not present a failed attempt at boronic acid salt production, they merely show decomposition products when boronic acids are treated at elevated temperature in basic conditions. If anything one skilled in the art would learn from Wu to avoid high temperatures in making the boronic acid salt as to avoid degradation of the product.

Adams et al.

Although applicant is correct in pointing out that the compounds of Adams do not encompass the instantly claimed boronic acid, Adams was relied upon for the teaching that numerous salts of boronic acids have been taught in the art and that boronic acid salt of the compound of Rewinkel is therefore not considered novel. Adams does

include imino acids and amino acid in the compound of formula 1(a) when R and R1 are linked to form a ring and X1 is "-CO-NH-".

Motivation for making the boronic acid salt

Applicant argues that the Examiner has failed to provide evidence that one skilled in the art would have been motivated to make a boronic acid salt of the compound in the instant claims (Pages 16-17 of the remarks).

Examiner disagrees. It is well known in the art to make salts of known acids. Boronic acid is clearly different from the conventional carboxylic acids that are more commonly encountered in the art, however Nanteuil et al. and Adams et al. are used to show that boronic acid salts, including base addition, of pharmaceutically active agents are known. Motivation for making a boronic acid salt would be the same as for making carboxylic acid salt. In addition, the instability of free Boronic acids is well established as evidenced by the two declarations submitted by the applicant. This well known instability of the free boronic acid serves as additional motivation to prepare the salt.

In his declaration, Dr, Marsden explains that boronic acids are usually stabilized by a strong Lewis base or protected as an ester. However, Adams et al. and Nanteuil et al. clearly point one skilled in the art to using a boronic acid salt as an alternative. One skilled in the art would therefore be free to choose from the three alternatives. The fact that boronic acid salts might be more difficult to make than the ester plays no role in deciding if the salt is obvious. One skilled in the art would try to mix the boronic acid with the appropriate metal hydroxide to make the salt. In view of Wu et al. one skilled in the art would know to keep the temperature below 70degC in order to avoid

decomposition. This is a well known procedure for making salts and as evidenced by applicants examples works just as well for making salts of boronic acids.

Rewinkel teaches the acid not the ester

Applicant argues that Rewinkel teaches the ester, not the acid of the instant compound.

Rewinkel teaches the acid. Even though the reference Rewinkel relies upon, Deadman et al, teaches the ester, Rewinkel chooses to depict an acid. Deadman teaches preparation of the ester of Boronic acid. One skilled in the art is aware that the ester is a protecting group for the boronic acid moiety and that that ester is dissociated in situ. Rewinkel depicts the free acid because it's the acid that possesses the desired pharmacological effect. While Deadman chooses to make an ester to protect the boronic acid from degradation, one skilled in the art need not follow Deadmans' example and is free to choose to make a salt of a pharmaceutical ingredient as is taught by Adams et al. and Nanteuil et al. Rewinkel does not teach preparation of the boronic acid compounds, but rather focuses on their pharmacological activity recognizing that the active form of the agent is the free acid form, the compounds are depicted as such.

The Marsden Declaration

The Declaration by Dr. Marsden has been fully considered. Dr. Marsden recognizes that boronic acids are oxidatively unstable (paragraph 5), describes common techniques to overcome the instability of the free boronic acids (paragraph 6). In paragraph 10, Dr. Mardsen describes what his approach to stabilizing TRI50c would be.

Although Dr. Marsdens' input concerning the pending claims is appreciated, the declaration was found to be insufficient to overcome the rejection of record. Dr. Marsdens' approach to stabilization of TRI50c is only one of several methods suggested in the art. The art clearly teaches stabilizing boronic acids as salts and one skilled in the art would have been free to choose from a limited number of available methods. Simply because formation of the salt might be considered more difficult that formation of the ester is not reason enough to dismiss the salt as a legitimate method of stabilizing a boronic acid.

In paragraph 16 Dr. Marsden draws a conclusion that the compound of Rewinkel is an ester protected boronic acid. This conclusion is based on the disclosure of that same compound in Deadman. As discussed above, Rewinkel is depicting the active form of the compound not the ester stabilized form. Deadman merely provides a method of stabilizing the free boronic acid as an ester, one skilled in the art can choose a different method of stabilizing the boronic acid depicted by Rewinkel, for example as a boronic acid salt.

Double Patenting

Claims 14-22, 37, 38, 40-55, 57, 59-72 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-21, 23, 25, 50-56 and 71-73 of U.S. Patent No. 7,112,572 ('572). Although the conflicting claims are not identical, they are not patentably distinct from each other

because the all the limitations of the instant claims are found in the sited claims of ('572).

Instant claims are directed to a pharmaceutically acceptable base addition salt of a boronic acid of formula (I) in claim 1, or formula (II) in claim 14, to formulation of the said salt in claims 26-28, pharmaceutical formulations in claims 50-56, anhydride comprising salts in claims 71-73.

Claim 2 of '572 claims a structure that encompasses the structure of the instant claim 1. Claim 12 of '572 displays a structure that is identical compound of formula (II) in the instant claim 14. Claims of '572 that directed to a salt and are dependent on claims 2 and 12 have all of the limitations of the instant claims 1-23 and 30-38. The formulations and medicament claimed in the instant claims 26-28 are obvious over claims 20, 23 and 25 of '572. The said formulation and medicament claims differ from the instant invention in that the compounds from which the formulation and medicament is made are not identical to the compound in '572. However, compound (III) of '572 encompasses all of the instantly claimed compounds, and compound (IV) of '572 is specie of the instantly claimed compound (I).

Conclusion

Claims 14-22, 37, 38, 40-55, 57, 59-72 are pending.

Claims 14-22, 37, 38, 40-55, 57, 59-72 are rejected.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

This action is a **final rejection** and is intended to close the prosecution of this application. Applicant's reply under 37 CFR 1.113 to this action is limited either to an appeal to the Board of Patent Appeals and Interferences or to an amendment complying with the requirements set forth below.

If applicant should desire to appeal any rejection made by the examiner, a Notice of Appeal must be filed within the period for reply identifying the rejected claim or claims appealed. The Notice of Appeal must be accompanied by the required appeal fee.

If applicant should desire to file an amendment, entry of a proposed amendment after final rejection cannot be made as a matter of right unless it merely cancels claims or complies with a formal requirement made earlier. Amendments touching the merits of the application which otherwise might not be proper may be admitted upon a showing a good and sufficient reasons why they are necessary and why they were not presented earlier.

A reply under 37 CFR 1.113 to a final rejection must include the appeal from, or cancellation of, each rejected claim. The filing of an amendment after final rejection, whether or not it is entered, does not stop the running of the statutory period for reply to the final rejection unless the examiner holds the claims to be in condition for allowance. Accordingly, if a Notice of Appeal has not been filed properly within the period for reply, or any extension of this period obtained under either 37 CFR 1.136(a) or (b), the application will become abandoned.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yevgeny Valenrod whose telephone number is 571-272-9049. The examiner can normally be reached on 8:30am-5:00pm M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Daniel Sullivan can be reached on 571-272-0779. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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